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Fluoxetine as disease modifying treatment in multiple sclerosis

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Abstract

The selective serotonin reuptake inhibitor (SSRI) fluoxetine, which is registered for a variety of psychiatric disorders, has been found to stimulate the cAMP responsive element binding protein (CREB), increase the production of brain-derived neurotrophic factor and the neurotrophic peptide S100 β , enhance glycogenolysis in astrocytes, block voltage-gated calcium and sodium channels, and decrease the conductance of mitochondrial voltage-dependent anion channels. These mechanisms of actions suggest that fluoxetine may also have potential for the treatment of a number of neurological disorders. We performed a Pubmed search to review what is known about possible therapeutic effects of fluoxetine in animal models and patients with neurological disorders. Beneficial effects of fluoxetine have been noted in animal models of stroke, multiple sclerosis and epilepsy. Fluoxetine was reported to improve neurological manifestations in patients with Alzheimer's disease, stroke, Huntington's disease, multiple sclerosis, traumatic brain injury and epilepsy. Clinical studies so far were small and often poorly designed. Results were inconclusive and contradictory. However, the available preclinical data justify further clinical trials to determine the therapeutic potential of fluoxetine in neurological disorders.

Introduction

The selective serotonin reuptake inhibitor (SSRI) fluoxetine is widely used to treat depression, obsessive-compulsive disorder, bulimia and panic disorder. It became FDA approved in 1987.¹ Fluoxetine increases extracellular serotonin (5-HT), which activates 5-HT receptors. The 5-HT receptors are classified into 7 classes (5-HT 1 to 7) with many subclasses. The effect of activation of 5-HT receptors is diverse and dependent on the class of receptor. The 5-HT system is complex and subject to continuing research.² Fluoxetine was also found to stimulate 5-HT₂ receptors directly.^{3,4}

Although the precise mechanism for its beneficial effects in psychiatric disorders is uncertain, fluoxetine has been shown to modulate important cellular functions that are thought to be important for neuronal cell survival and neuroplasticity, including the regulation of the transcription factor cAMP response element binding protein (CREB), the production of neurotrophic factors, the regulation of neuronal energy supply, and the opening and closing of ion channels.

The aim of this article is to give an overview of the neurobiological effects of fluoxetine that could be useful for the treatment of neurological disorders, and to review the reported effects of fluoxetine on neurological disorders and their animal models. We performed a PubMed search with the words fluoxetine, and neurologic(al), neuroprotection, Alzheimer's disease, dementia, Parkinson's disease, multiple sclerosis, stroke, Huntington's disease, epilepsy and brain injury. Articles only reporting effects on psychiatric symptoms were excluded. All available English written reports of animal and patient studies published online before May 2007 were included.

Neurobiological effects

An overview of the articles reporting on the neurobiological effects of fluoxetine that could be useful for the treatment of neurological disorders is shown in table 1 (page 20).

Effects on CREB and neurotrophic factors

Chronic treatment with fluoxetine upregulates cerebral CREB expression and phosphorylation in rats and mice.^{5,6,7} CREB is a transcription factor, which induces the expression of genes with roles in cell survival, energy metabolism and regeneration.⁸ This transcription factor is so important that the search for drugs that increase CREB levels has been called the search for the 'Holy Grail of neurological therapeutics'.⁹

One of the CREB regulated genes is coding for brain-derived neurotrophic factor (BDNF). BDNF is important for the normal development of the human brain and has a critical role in neural plasticity.^{10,11} Decreased levels of BDNF may play a pivotal role in the

neurodegeneration associated with aging, Huntington's disease, and Alzheimer's disease.¹⁰ Increased BDNF expression was found in multiple sclerosis lesions and proposed as a mechanism for neuroprotection.¹² Fluoxetine elevates the concentrations of BDNF in rat brain,¹³ and enhances the production of S100 β in astrocytes.^{14,15} S100 β , which is mainly produced in astrocytes, has paracrine and autocrine effects on neurons and glia. It enhances neurogenesis, but leads to apoptosis in high concentration.¹⁶ S100 β elevation is associated with treatment response in multiple sclerosis patients on interferon- β , and S100 β administration in an in vitro model of traumatic brain injury reduced delayed neuronal injury.^{17,18}

Effect of fluoxetine on neuronal energy supply

The energy supply of neurons is complex and incompletely understood. According to the astrocyte-neuron lactate shuttle hypothesis, lactate produced from astrocyte glycogenolysis is shuttled to neurons and axons and serves as metabolic fuel, especially during neuronal activation.^{19,20,21} Fluoxetine is able to enhance glycogenolysis in cultured astrocytes and could thus theoretically improve energy supply of axons and neurons.^{3,4,22}

Effect of fluoxetine on electrolyte channels

Fluoxetine inhibits voltage-gated calcium channels in rat cerebral cells and sodium channels in bovine adrenal cells.^{23,24} This may prevent neurotoxic intracellular calcium overload in neurons, which is a key mechanism in neuronal death in both acute conditions, such as ischemia and hypoxia, and neurodegenerative processes.^{25,26,27} In ischemic rat spinal cord, white matter inhibition of the Na⁺/Ca²⁺-exchanger was found to be neuroprotective.²⁸

Fluoxetine decreased the conductance of the mitochondrial voltage-dependent anion channel (VDAC) in mitochondria isolated from rat liver.²⁹ VDAC has an important role in the release of cytochrome c, an important step in apoptosis. Inhibition of the VDAC by fluoxetine protected against staurosporine-induced apoptotic cell death in human U-937 cells.^{29,30}

Studies in neurological disorders and their animal models

An overview of the articles reporting effects of fluoxetine in animal models of neurological disorders and in patients with neurological disorders is given in tables 2 (page 22) and 3 (page 25).

Parkinson's disease

In patients with Parkinson's disease neuronal destruction of the substantia nigra reduces the amount of dopamine in the striatum, which impairs motor function. Neuronal cell death may be caused by mitochondrial dysfunction resulting in decreased energy production and increased intracellular Ca^{2+} levels.³¹ Fluoxetine might be neuroprotective by preventing elevations of intracellular Ca^{2+} levels, promoting neuronal energy supply and the release of neurotrophic factors by astrocytes.

In a rat model of Parkinson's disease, fluoxetine reduced the availability of extracellular dopamine after L-DOPA administration, and it was suggested that SSRIs might worsen motor function in patients with Parkinson's disease.³²

In agreement with this observation, a number of case reports and small studies suggested that fluoxetine may worsen motor symptoms in Parkinson's disease.^{33,34} However, an open pilot study in 14 patients who used fluoxetine 20 mg daily for 1 month found no change in rigidity and bradykinesia scores, but a decrease in tremor severity was observed.³⁵ Another open label study of 62 depressed patients with Parkinson's disease showed that SSRIs were well tolerated and did not change motor symptoms as measured with the Unified Parkinson's Disease Rating Scale (UPDRS) after 6 months of treatment.³⁶

In three reports the effects of repetitive transcranial magnetic stimulation (rTMS) and fluoxetine in depressed patients with Parkinson's disease were compared. Both fluoxetine and rTMS improved the Stroop (coloured words and interference card) and Hooper and Wisconsin (perseverative errors) test performances. Increases in regional cerebral blood flow (rCBF) in the posterior cingulate gyrus and decreases in the right medial frontal gyrus were noted with both fluoxetine and rTMS. Compared with rTMS, fluoxetine intake was associated with a relative rCBF increase in the occipital lobe.^{37,38} The Mini Mental State Examination (MMSE),³⁹ which is an 11-item examination of cognitive functions with higher scores indicating better cognition, improved when both groups were analyzed together after 8 weeks. The motor score did not change significantly although there was a trend towards worsening in the fluoxetine group.⁴⁰

Alzheimer's disease

In Alzheimer's disease amyloid- β and tau make up the plaques and tangles that are believed to cause the progressive neurodegeneration, which leads to dementia. Impaired energy metabolism is found in Alzheimer's disease, and an increase in CREB phosphorylation has been suggested to offer promise as therapeutic intervention for counteracting neuronal damage in Alzheimer's disease.^{41,42}

In a small randomized, double-blind trial, 18 patients with Alzheimer's disease and major depression were treated with fluoxetine 10 mg/day and 19 with amitriptyline 25 mg/day during 6 weeks.⁴³ Scores on the MMSE increased significantly with treatment when both

groups were analyzed together. In the fluoxetine group the MMSE increased from 20.0 at baseline to 21.4 at day 45. Dropout rates were very high; 55% for amitriptyline and 22% for fluoxetine. A randomized, double-blind trial compared the use of fluoxetine 20 mg/day, haloperidol 3 mg/day and placebo in 15 non-depressed patients with disruptive agitated behaviors (5 per group) over a period of 6 weeks.⁴⁴ Besides more side-effects in the active treatment groups no significant differences were found.

No improvement of MMSE was noticed in a randomized, double-blind, placebo-controlled trial of 15 depressed patients on fluoxetine up to 40 mg/day during 6 weeks.⁴⁵

In a 8-week, double-blind, placebo-controlled study of 58 non-depressed patients with mild cognitive impairment, which may be a prodromal state of Alzheimer's disease, fluoxetine improved memory and cognition, measured with the MMSE and subtests from the Persian standardized Wechsler Memory Scale III (WMS-III).⁴⁶

Stroke

In ischemic stroke neurons die when blood supply falls below the infarction threshold of 8-10 mL/100 mg/ min. Neurons in the so-called penumbra, where the blood flow is between the infarction threshold and the functional threshold of 18-22 mL / 100g/ min, can die due to lethal biochemical processes or be rescued by vessel recanalisation or neuroprotective interventions. Recovery after stroke is not only dependent on the survival of the neurons in the penumbra, but also on brain plasticity. Fluoxetine could be neuroprotective in the acute phase (ion channel blocking, enhanced energy metabolism and neurotrophic factor release) and improve brain plasticity during stroke rehabilitation (neurotrophic factors).

After induction of focal ischemia in rats, fluoxetine did not alter the degree of recovery of function compared to non-treated rats after 4 weeks of treatment.⁴⁷ In another study, fluoxetine administered 7 days before and up to 28 days after induction of focal cerebral ischemia did not influence sensorimotor recovery in rats.⁴⁸ However, low dose fluoxetine given during 7 days post-partum reduced functional deficits in rats with neonatal hypoxic ischemic brain injury.⁴⁹

In 8 non-depressed stroke patients, a single dose of fluoxetine appeared to improve motor skills of the affected side.⁵⁰ During rehabilitation 1 to 6 months after stroke, severely disabled patients showed significantly more often good recovery after 3 months of fluoxetine treatment, compared to placebo and the norepinephrine reuptake inhibitor maprotiline.⁵¹ Two other randomized, double-blind, placebo-controlled trials including 104 and 31 stroke patients were mainly focused on the antidepressant effects of fluoxetine and found no benefit on functional recovery after respectively 45 days and 12 weeks of treatment.^{52,53}

Spalletta et al. looked at the effect of sertraline (n=21) and fluoxetine 20 mg (n=29) on patients with and without alexithymia, a condition in which patients have problems identifying and coping with feelings. A significant increase of MMSE after 8 weeks of treatment in the 32 patients without alexithymia was noticed.⁵⁴

Huntington's disease

In patients with Huntington's disease the slowly progressive neuronal loss in the basal ganglia causes a movement disorder (characteristic chorea) together with a cognitive and affective disorder. An altered energy metabolism is hypothesized to be important in the pathophysiology of Huntington's disease.⁵⁵ Fluoxetine might have a neuroprotective effect by increasing energy metabolism and the production of BDNF.

Two patients with Huntington's disease responded well to fluoxetine treatment. Both showed motor improvement and one patient's cognitive functions also improved. Beneficial effects did take 4-6 months to develop and lasted several years.⁵⁶ A randomized, double-blind, placebo-controlled trial in non-depressed Huntington's disease patients failed to show substantial clinical benefits of fluoxetine treatment after 4 months, although a slight reduction in agitation and in the need for routine care was found.⁵⁷

Multiple sclerosis

In the beginning of their disease about 80% of the patients with multiple sclerosis have symptoms that come and go (relapses) resulting from focal inflammatory demyelination in the central nervous system (CNS). After 10 to 20 years most patients experience gradual increasing disability, which is caused by a more diffuse progressive axonal loss. Mitochondrial failure, which gives dysfunction of electrolyte channels and leads eventually to toxic intracellular calcium overload, is suspected to play a pivotal role in the axonal dysfunction and degeneration in multiple sclerosis.⁵⁸ By improving energy metabolism and by blocking sodium channels, fluoxetine might protect axons in patients with multiple sclerosis.

In mice with chronic relapsing experimental allergic encephalomyelitis (EAE), an animal model for the inflammatory lesions of multiple sclerosis, fluoxetine prevented worsening of neurological signs, prolonged survival, and reduced CNS inflammation and axonal damage compared to untreated animals.⁵⁹

In a letter to the editor a psychiatrist reported a patient with multiple sclerosis who suffered a worsening of symptoms after initiating treatment with fluoxetine.⁶⁰ A number of psychiatrists replied that multiple sclerosis patients on treatment with fluoxetine on the contrary remained quite stable.⁶¹

In a preliminary open study of 11 patients with multiple sclerosis, 2 weeks of fluoxetine administration increased cerebral white matter N-acetylaspartate levels on magnetic resonance spectroscopy, suggesting an improvement in axonal mitochondrial energy production.⁶² Trends towards an improvement of walking ability and fatigue were also noted.

Traumatic brain injury

Trauma to the head causes permanent and reversible damage to neurons. Improved energy metabolism and increased production of neurotrophic factors by the administration of fluoxetine might prevent irreversible loss of neurons and promote plasticity in patients with traumatic brain injury.

In a rat model of moderate to severe traumatic brain injury, fluoxetine treatment during 15 days did not improve motor performance.⁶³

In an open-label investigation of 5 head-injured patients, fluoxetine not only improved mood, but had also a beneficial effect on several measures of cognition after 8 months of treatment.⁶⁴

Epilepsy

Epilepsy is caused by a reduced membrane stability of neurons. Both genetic predisposition and neuronal damage increase the susceptibility for epileptic seizures. Treatment is aimed at increasing the membrane stability. By blocking sodium and calcium channels fluoxetine might improve membrane stability.

Fluoxetine reduced seizure activity in many animal models of epilepsy.^{65,66,67,68,69,70} However, one study reported an increase in epileptic activity after treatment with fluoxetine in a rat epilepsy model.⁷¹

In an open-label, add-on trial of fluoxetine in patients with complex partial seizures with and without secondary generalization, 6 patients showed complete disappearance of their seizures and the remaining 11 patients had a 30% reduction in seizure frequency.⁷²

It is stated that despite some case reports of worsening of seizure activity, antidepressant drugs can have anticonvulsant effects when used in usual dosages.^{73,74}

Discussion

Caution should be taken to extrapolate the results of in vitro studies to in vivo effects. In cell cultures the concentration of fluoxetine used (1-50 μ M) mostly exceed therapeutic plasma levels in patients (1-3 μ M) and the effect of fluoxetine might be overestimated.

However, drug concentrations of fluoxetine in the human brain are reported to be 20 fold higher than plasma levels⁷⁵ and concentrations of up to 50 μ M might thus be reached in the human brain.

Beneficial effects of fluoxetine were noted in animal models of stroke, multiple sclerosis and epilepsy. In these studies higher dosages of the medication (1.0 -20 mg/kg/day) were used than in clinical use (20-80 mg/day; = 0.25 – 1.0 mg/kg/day) and the results must therefore also be regarded cautiously. In patients with Parkinson's disease, fluoxetine was well tolerated but no positive effects on symptoms of the disease process were reported. In Alzheimer's disease one positive study was found in mild cognitive impairment. The other studies had only 6 weeks of follow-up and could not find beneficial effects. In stroke patients initial claims of a beneficial effect of fluoxetine on motor recovery could not be confirmed in a larger study with longer follow-up. In Huntington's disease a relatively large, well-designed trial with 4 months of follow-up could not find better performance of patients treated with fluoxetine compared to placebo-treated patients. In epilepsy, multiple sclerosis and traumatic brain injury good studies are lacking.

Many clinical studies were performed in depressive patients, and it is uncertain whether improvement of neurological symptoms was influenced by improvement of the underlying depression. Also it is difficult to measure effects in neurodegenerative disorders since progression is slow, clinical scales are insensitive and good surrogate markers are lacking. Underestimation of therapeutic effect is possible since at least several weeks of treatment are necessary before plasma levels of fluoxetine become stable.⁷⁶

Small studies with a number of other SSRIs have also shown an indication for a possible beneficial effect in some neurological disorders: paroxetine and citalopram in patients with Parkinson's disease,^{77,78} sertraline in patients with traumatic brain injury,⁷⁹ and citalopram and fluvoxamine in patients with epilepsy.^{80,81,82,83,84} Since distinct SSRIs have different affinities for the serotonin receptors it is not possible to generalize the results of fluoxetine to all other SSRIs.

Although clinical studies so far are inconclusive, the preclinical findings justify further trials with fluoxetine and perhaps other SSRIs in patients with neurological disorders.

Table 1 Overview of in vitro studies examining neurobiological effects of fluoxetine.

Article	Cells/animals	Intervention	Duration of treatment/ follow-up	Results
Chen et al, 1995 ³	Cultures of astrocytes of mice	Fluoxetine 10^{-7} to 10^{-4} M Serotonin 10^{-11} to 10^{-5} M	Acute to 1 week	Acute increase in glycogenolysis with both fluoxetine and serotonin; chronic no change glycogenolysis with fluoxetine and increase with serotonin Inhibition of voltage gated calcium channels
Deak et al, 2000 ²³	Hippocampal pyramidal cells of rats	Fluoxetine 3 μ M	Acute	
Haring et al, 1993 ¹⁴	15 male rats	5 rats fluoxetine 35 mg/kg/day; 5 rats parachlorophenylalanine (5-HT inhibitor); 5 rats placebo	1 week	About 85% reduction in S100 β with parachlorophenylalanine and 7% increase of S100 β with fluoxetine
Kong et al 2002 ⁴	Cultures of astrocytes of mice	Fluoxetine 10 μ M	Short term (1 week) long term (2-3 weeks)	Short term decrease glycogenolysis, long term increase glycogenolysis
Manev et al, 2001 ¹⁵	Rats, hippocampus	Fluoxetine 5 mg/kg /day	21 days	Increase S100 β
Mercier et al, 2004 ¹³	Cultures of astrocytes of rats	Fluoxetine 40 μ M	2 hours	Increase BDNF lasting for several days

Table 1 continued

Article	Cells/animals	Intervention	Duration of treatment/ follow-up	Results
Nahon et al, 2005 ²⁹	Mitochondria from rat liver	Fluoxetine 10, 20 and 50 μ M	Acute	Dose related decrease of the VDAC, inhibition of opening of the mitochondrial permeability pore, inhibition of the release of cytochrome c and protection against staurosporine-induced apoptotic cell death
Nibuya et al 1996 ⁷	Rats, hippocampus	Fluoxetine 5 mg/kg /day	21 days	Increased expression CREB mRNA and expression of BDNF
Pancrazio et al, 1998 ²⁴	Bovine adrenal chromaffin cells	Fluoxetine 20 μ M	Acute	Decrease of voltage gated Na^+ current by 61%
Thome et al, 2000 ⁵	Transgenic mice with a CRE-LacZ reporter gene construct	Fluoxetine 10 mg/kg/day	14 days	Increase in CRE mediated gene expression and phosphorylation of CREB in cerebral cortex, hippocampus, amygdale and hypothalamus
Tiraboschi et al, 2004 ⁶	12 male rats, hippocampus and whole frontal lobe	Fluoxetine 10 mg/kg/day	Acute (3hrs) chronic (14 days)	Chronic treatment increased the phosphorylation of CREB
Zhang et al, 1993 ²²	Cultures of astrocytes of mice	Fluoxetine 10 μ M	10 min	Increase glycogenolysis

BDNF = Brain derived neurotrophic factor; VDAC = voltage-dependent anion channel; CREB = cAMP response element binding protein

22 **Table 2** overview of studies reporting results of the effects of fluoxetine in animal models of neurological disorders.

Article	Animal model	Intervention	Follow-up	Results
Chang et al, 2006 ⁴⁹	Neonatal hypoxic-ischemic brain injury model of rat pups	Fluoxetine 5, 15 mg/kg/day for 7 days, at day 7 hypoxic-ischemic injury	33-35 days	5 mg/kg fluoxetine treatment reduced functional deficits and increased levels of phosphorylated CREB and BDNF gene expression in hippocampus and cortex; 15 mg/kg had no effect
Kecskemeti et al, 2005 ⁷⁰	Pentylenetetrazol-induced mouse epilepsy model	Fluoxetine 5, 10, 20 mg/kg; norfluoxetine 5, 10, 20 mg/kg; phenytoin 30 mg/kg; clonazepam 0.1 mg/kg; control	60 minutes	Norfluoxetine and fluoxetine 20mg/kg increase survival compared to controls; survival is comparable to effect of phenytoin
Perićić et al, 2005 ⁶⁷	Epilepsy mouse model (Convulsions elicited with picrotoxin)	Fluoxetine 20 mg/kg/day both after stress and no stress	1 - 5 days	Both acute and prolonged administration of fluoxetine increased the convulsion threshold in stressed and unstressed mice
Prendiville et al, 1993 ⁶⁸	Rat model of focally evoked complex partial seizures secondary generalized	Fluoxetine 5, 10, 20 mg/kg	1 day	Fluoxetine 5 mg/kg 50% protection, higher protection with higher doses
Richman et al, 2007 ⁶⁶	Seizure susceptible EI mice	Fluoxetine 10 mg/kg/day	3 - 7 days	No effect after 3 days; after 7 days no seizures in fluoxetine treated mice compared to 40% of mice with seizures in control groups

Table 2 continued

Article	Animal model	Intervention	Follow-up	Results
Traugott and Trejo, 1997 ⁵⁹	Mice with established chronic Experimental Allergic Encephalomyelitis	Fluoxetine 1 mg/kg/day	3 months	Fluoxetine treated mice showed less worsening of neurological signs, survived longer and had less CNS inflammation and axonal damage
Ugale et al, 2004 ⁶⁹	Pentylenetetrazol-induced mouse epilepsy model	Fluoxetine 1, 5, 10, 20 mg/kg	60 min	Dose dependent effect of protection against seizures (small effect 5 mg/kg [20% protection]; large effect in 20 mg/kg [100% protection])
Wada et al, 1995 ⁶⁵	Hippocampal seizures elicited by electrical stimulation in a rat model	Fluoxetine 10 mg/kg/day: single dose and injection after 21 days treatment followed by 7 days no drug	1-28 days	After discharge threshold increased after 21 days pretreatment with fluoxetine, acute no effect
Wilson and Hamm, 2002 ⁶³	Rat model of traumatic brain injury	Fluoxetine 2.5, 5.0, 10.0 mg/kg/day	1-15 days postinjury	No effect on motor and cognitive function
Windle and Corbett, 2005 ⁴⁷	Focal induced ischemia in rats	Fluoxetine 10 mg/kg/day	4 weeks	No effect on functional recovery
Yamato et al, 2001 ³²	Rats with nigrostriatal denervation	Fluoxetine 10 mg/kg	300 min	41% reduction in cumulative amount of extracellular dopamine

Table 2 continued

Article	Animal model	Intervention	Follow-up	Results
Zhao et al, 2005 ⁴⁸	Focal induced ischemia in rats	Fluoxetine 5 mg/kg/day (7 days before ischemia and 28 days after)	28 days	No effect on histological and behavioral outcome
Zienowicz et al, 2005 ⁷¹	Pentylenetetrazol-induced mouse epilepsy model	Fluoxetine 10 mg/kg	30 minutes	Number of rats with seizures higher in fluoxetine treated group (100% versus 50%)

CREB = cAMP response element binding protein; BDNF = Brain derived neurotrophic factor; CNS = central nervous system

Table 3 overview of clinical studies with fluoxetine in patients with neurological disorders.

Article	Subjects	Intervention	Study design	Follow-up time	Results (on neurological function)
Auchus et al. 1997 ⁴⁴	15 non-depressed pt with Alzheimer's disease and disruptive agitated behaviors	5 pt fluoxetine 20 mg/day; 5 pt haldol 3 mg/day; 5 pt placebo	Double-blind	6 weeks	No effect on Cohen-Mansfield Agitation Inventory and no effect on sum of scores of sections C, D and E of the behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and total score on the Caregiver Stress Inventory (CSI)
Boggio et al. 2005 ^{*37}	31 pt with Parkinson's disease and depression	13 pt active rTMS and placebo; 12 pt sham rTMS and fluoxetine 20 mg/day; 6 pt no treatment	Double-blind	8 weeks	Significant improvement of Stroop and Hooper and Wisconsin test performances in the pt on treatment
Browning 1990 ⁶⁰	1 pt with multiple sclerosis	unknown	Observational	4 days	Severe worsening symptoms of multiple sclerosis
Como et al. 1997 ⁵⁷	30 non-depressed pt with Huntington's disease	17 pt fluoxetine 20 mg/day; 13 pt placebo	Double-blind, placebo-controlled	4 months	No differences in total functional capacity (TFC), neurological and cognitive ratings

Table 3 continued

Article	Subjects	Intervention	Study design	Follow-up time	Results (on neurological function)
Dam et al. 1996 ⁵¹	52 pt with hemiplegic stroke (< 6 months)	18 pt fluoxetine 20 mg/day; 17 pt maprotiline 150 mg/day; 17 pt placebo	Double-blind, placebo-controlled	3 months	Trends towards more improvement in walking and activities of daily living capacities in fluoxetine group; more pt with good recovery in fluoxetine group
Dell' Agnello et al. 2001 ³⁶	62 pt with Parkinson's disease and depression	16 pt fluoxetine 20 mg/day; 15 pt citalopram 20 mg/day; 16 pt fluvoxamine 150 mg/day; 15 pt sertraline 50 mg/day	Open	6 months	No change UPDRS
De Marchi et al. 2001 ⁵⁶	2 pt with Huntington's disease	Fluoxetine 20 mg	Observational	6 years and 2 year	Improvement in choreatic movements and stability/improvement in MMSE. Improvements did take up to 6 months to appear
Favale et al. 2003 ⁸⁰	17 pt with complex partial epileptic seizures	Fluoxetine 20 mg/day	Open	14 ± 1.1 months	Complete disappearance of seizures in 6 pt, lowering in seizure frequency by 30% in other patients
Flax et al. 1991 ⁶¹	20 pt with multiple sclerosis	unknown	Observational	2-21 months	No worsening symptoms, several patients with improvement in neurological function

Table 3 continued

Article	Subjects	Intervention	Study design	Follow-up time	Results (on neurological function)
Fregni et al. 2004 ^{*40}	42 pt with Parkinson's disease and depression	21 pt active rTMS and placebo; 21 pt sham rTMS and fluoxetine 20 mg/day	Double-blind	8 weeks	MMSE improvement in both groups; tendency for worse motor UPDRS scores in fluoxetine group
Fregni et al. 2006 ^{*38}	26 pt with Parkinson's disease and depression; 29 healthy age-matched controls	13 pt active rTMS and placebo; 13 pt sham rTMS and fluoxetine 20 mg/day	Double-blind	8 weeks	Increase in rCBF in the posterior cingulate gyrus and decreases in the right medial frontal gyrus with both treatments; a relative rCBF increase in the occipital lobe with fluoxetine
Horsfield et al. 2002 ⁶⁴	5 pt with traumatic brain injury with no or moderate depression	Fluoxetine 20-60 mg/day	Open	8 months	Better performance on Trail Making Test Part A, an attentional-motor speed task and the letter-number sequencing subtest of WAIS-III, reflecting working memory
Montastruc et al. 1995 ³⁵	14 pt with Parkinson's disease	Fluoxetine 20 mg/day	Open	1 month	No change UPDRS, reduction of tremor
Mostert et al. 2006 ⁶²	11 pt with multiple sclerosis	Week 1 fluoxetine 20 mg; Week 2 fluoxetine 40 mg	Open	2 weeks	Increase of NAA/Cr on MRS; trends towards improvement of walking ability and fatigue

Table 3 continued

Article	Subjects	Intervention	Study design	Follow-up time	Results (on neurological function)
Mowla et al. 2007 ⁴⁶	58 non-depressed pt with mild cognitive impairment	33 pt fluoxetine 20 mg/day; 25 pt placebo	Double-blind, placebo-controlled	8 weeks	High drop out rate (10 pt on fluoxetine group, 4 in placebo group). Significant improvement of MMSE and logical memory (from the Persian standardized Wechsler Memory Scale III) in fluoxetine group
Pariente et al. 2001 ⁵⁰	8 non-depressed pt with pure motor stroke	Single dose fluoxetine 20 mg and single dose placebo	Double-blind, crossover, placebo-controlled	5 hours	Under fluoxetine, during active motor task, hyperactivation in the ipsilesional primary motor cortex shown with fMRI and improvement of motor skills of the affected side
Petracca et al. 2001 ⁴⁵	41 pt with probable Alzheimer's disease and depression	17 pt fluoxetine 40 mg/day; 24 pt placebo	Double-blind, placebo-controlled	6 weeks	No effect of fluoxetine on MMSE and FIM
Robinson et al. 2000 ⁵²	104 pt with acute stroke (< 6 months), 56 were depressed	40 pt fluoxetine 40 mg/day; 31 pt nortriptyline 100 mg/day; 33 pt placebo	Double-blind, placebo-controlled	12 weeks	Nortriptyline improved FIM compared to fluoxetine; no differences in change MMSE
Simons 1996 ³⁴	5 pt with Parkinson's disease	4 pt fluoxetine 20 mg/day; 1 pt fluoxetine 10 mg/day	Observational	1 month	UPDRS increase of 20-25% in 2 pt

Table 3 continued

Article	Subjects	Intervention	Study design	Follow-up time	Results (on neurological function)
Spalletta et al. 2006 ⁵⁴	50 pt with poststroke major depression, 18 with alexithymia	29 pt fluoxetine 20-40 mg/day; 21 pt sertraline 50-100 mg/day	Open	8 weeks	Pt without alexithymia had a significant increase in MMSE
Steur 1993 ³³	4 pt with Parkinson's disease and depression	Fluoxetine 20 mg/day	Observational	8-11 weeks	Significant increase UPDRS during treatment
Taragano et al. 1997 ⁴³	37 pt with Alzheimer's disease and major depression	18 pt fluoxetine 10 mg/day; 19 pt amitriptyline 25 mg/day	Double-blind	45 days	For total group significant increase in MMSE, no difference between fluoxetine and amitriptyline
Wíart et al. 2000 ⁵³	31 pt with hemiplegic stroke (< 3 months) with major depression	16 pt fluoxetine 20mg/day; 15 pt placebo	Double-blind, placebo-controlled	6 weeks	no difference in change in MMSE and change in FIM

pt = patients; UPDRS = unified Parkinson's disease rating scale; * = reports on the same patients; rCBF = regional cerebral blood flow; rTMS = repetitive transcranial magnetic stimulation; MMSE = mini mental state examination; fMRI = functional magnetic resonance imaging; FIM = Functional Independence Measure

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Part 2

Conventional MRI studies

